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THE EFFECT OF β-ADRENERGIC RECEPTOR BLOCKING DRUGS ON CEREBRAL BLOOD FLOW

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1 Cerebral blood flow (CBF) was measured by the ^{133}xenon inhalation method in 33 newly-diagnosed hypertensive patients prior to commencing therapy.

2 Blood pressure was treated by using a varying sequence of four different drugs, namely labetalol, metoprolol, oxprenolol and sotalol, each of which is a β-adrenergic receptor blocking agent, but with differing additional properties.

3 CBF measurements were repeated when blood pressure was controlled. No significant change in CBF was found with any of the four drugs, in contrast to the fall which has been reported when drugs of this type are administered acutely.

Introduction

It is well-established that Raynaud's phenomenon is a side effect of treatment with β-adrenergic receptor blocking drugs (Marshall, Roberts & Barritt, 1976). However, blood flow has been shown to be reduced not only to limbs but also to other parts of the vascular tree, and it seems likely that this is an effect of the β-adrenergic receptor blockade itself, rather than simply an epiphenomenon (Nies, Evans & Shand, 1973).

The mechanisms by which cerebral blood flow (CBF) is regulated remain controversial. Local, metabolic factors were formerly thought to be of paramount importance (Kety, 1964) but more recently interest has centred around a possible role for neurogenic influences (Ponte & Purves, 1974; James & Macdonell, 1975a). Morphological (Dahl & Nelson, 1964; Iwayama, 1970; Iwayama, Furness & Burnstock 1970) and histochemical (Falck, Nielsen & Owman, 1968; Kajikawa, 1969; Ohgushi, 1968) evidence has been produced to show that cerebral vessels are innervated similarly to other vascular beds. Pharmacological studies have sought to elucidate the nature of this innervation and have indicated a number of different receptors including β_1 receptors in association with intracranial arteries in the cat (Edvinsson & Owman, 1975). It has further been shown by the same workers that the dilating effect of catecholamines on the vessel is blocked by propranolol.

Although there thus seems the potential for β-adrenergic receptor blocking drugs to influence CBF via a neurogenic mechanism, it should also be noted that catecholamines can stimulate carbohydrate metabolism in the brain as well as in peripheral tissues, and therefore blocking this action might reduce the overall metabolic rate so reducing CBF as a secondary phenomenon. Potentially, therefore, β-adrenergic receptor blocking drugs might reduce CBF by either or both of these mechanisms. That this does indeed occur acutely has been shown both in animals (Aoyagi, Deshmukh, Meyer, Kawamura & Tagashira, 1976; James & Macdonell, 1975b) and in man (Hares, James & Griffith, 1977). Hares *et al.* (1977) showed a mean fall in CBF from 47.1 to 40.9 ml 100 mg^{-1} min^{-1} (significant at 1% level on *t*-testing) when acebutolol was administered by intravenous infusion in a total dose of 0.2 mg/kg to seven normal volunteers, using the same technique for CBF measurement as will be described for this study.

It therefore seemed appropriate to investigate the situation obtaining when such drugs are used chronically, not only because of the clinical relevance, but also because it has been established that with regard to some measurements (e.g. cardiac output) the acute effects of β-adrenergic receptor blocking drugs differ from those in the chronic setting.

Methods

Newly-diagnosed outpatients with essential hypertension were considered for inclusion in the study. Hypertension was defined as a mean diastolic pressure of > 100 mm Hg (Korotkoff 4th sound) for

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blood pressure recordings measured on three separate occasions. Blood pressure was measured with a standard mercury sphygmomanometer with the patient supine for 5 min, and again after standing for 2 min. Patients were excluded if they had contraindications to β-adrenergic receptor blocking drugs; if they had concomitant systemic disease; if they were on any form of medication with the exception of thiazides which were permitted in a few cases; or if they were aged less than 18 years.

Informed consent was obtained from all patients and the study was approved by the hospital ethics committee.

Before commencing treatment with definitive antihypertensive therapy CBF was measured both at normocapnia and at hypercapnia, although the present paper is concerned only with the former. CBF was measured by the ^{133}xenon inhalation method of Wyper, Lennox & Rowan (1976). Details of the procedure have been described fully in a previous article (Dandona, James, Newbury, Woollard & Beckett, 1978). Patients were rested in the supine position and familiarized with the apparatus before measurements were commenced. End tidal CO_2 values were measured with a Beckman infrared CO_2 analyser.

Patients were then commenced on one of four β-adrenergic receptor blocking drugs selected for their varying ancillary properties which are outlined in Table 1. Each patient ideally received all four drugs, a latin square method being used to devise four orders of drugs which allowed all sequences of drugs to be covered in the study. Allocation of the initial drug was not formally randomized, but equal numbers of patients were allocated to each of the four groups. Standard, marketed formulations of the drugs were employed.

Patients were followed up by regular and frequent outpatient visits. Control of blood pressure was arbitrarily defined as diastolic pressure below 100 mm Hg on two occasions. CBF measurements were repeated when BP control had been achieved, when the next drug in the sequence was instituted, this pattern continuing until CBF had been measured on each of the four drugs. Patients took each drug for a minimum of 3 weeks before the CBF measurement, not only for the full effect of the drug to build up, but also to serve as a washout period for the previous drug.

Results

A total of 106 CBF measurements on drug at normocapnia were made on 33 patients. A variety of reasons accounted for the failure to obtain four readings on each patient. These included failure of follow up (partly due to departure from the catchment area and partly due to administrative failure) in six patients; discovery of pharyngeal carcinoma with associated severe dysphagia (one patient); failure to control BP satisfactorily (one patient). One patient sustained a stroke during the study. Two CBF curves proved technically unsatisfactory. No patients had to be withdrawn because of unacceptable side effects.

Of the 33 patients, 20 were female and 13 male with mean ages of 58 (range 35–77) years and 55 (range

Table 1 Properties of the four β-adrenergic receptor blocking drugs used in the study

	Cardioselective	*α-adrenoceptor blockade*	*ISA*	*MSA*
Labetalol	−	+	−	+
Metoprolol	+	−	−	−
Oxprenolol	−	−	+	+
Sotalol	−	−	−	−

(ISA = Intrinsic sympathomimetic activity. MSA = Membrane stabilizing activity).

Table 2 Mean blood pressures and doses for each of the four drugs used

	Mean arterial blood pressure (mm Hg)		*Diastolic pressure (mm Hg)*		*Total daily dose (mg)*
	Pre-drug	*On-drug*	*Pre-drug*	*On-drug*	*(Range)*
Labetalol	137	109	113	92	448 (200–900)
Metoprolol	138	113	115	95	296 (200–600)
Oxprenolol	139	116	116	96	253 (80–640)
Sotalol	137	114	114	95	312 (160–640)

Table 3 Values (mean ± s.e. mean) for cerebral blood flow and CO_2 for each of the four drugs used

	Cerebral blood flow (ml 100 mg^{-1} min^{-1})		*CO_2*	
	Pre-drug	*On-drug*	*Pre-drug*	*On-drug*
Labetalol (n =27)	45.1 (±1.1)	47.1 (±1.2)	32.6 (±1.3)	35.0 (±1.1)
Metoprolol (n =27)	45.4 (±1.0)	44.6 (±0.8)	32.0 (±1.3)	33.7 (±1.1)
Oxprenolol (n =27)	45.4 (±1.2)	46.7 (±1.3)	33.6 (±1.2)	34.9 (±1.3)
Sotalol (n =25)	45.6 (±1.0)	46.4 (±1.2)	32.9 (±1.4)	34.6 (±1.0)

37–76) years respectively. Comparable falls in blood pressure were achieved with each drug and these are shown on Table 2 together with the drug doses. CBF and CO_2 results are shown in Table 3. A slight increase in CBF at normocapnia is found with each drug except metoprolol, but with none of the drugs does the difference between predrug and on-drug readings reach statistically significant proportions (Student's t-test).

As mentioned previously, thiazide diuretics were permitted in a few cases (e.g. if the patient had been previously commenced on such medication by his own general practitioner) but analysis of the results excluding these patients likewise showed no significant change in CBF, nor was there any difference in the small group (5) who were on thiazides throughout.

Discussion

It has been reported (Aoyagi *et al.*, 1976; Hares *et al.*, 1977) that CBF falls when β-adrenergic blocking drugs are administered acutely. We wondered if in a more chronic setting this might also occur and be reflected clinically in the lethargy and lightedness which are known to occur on occasion in association with these drugs (Petrie, Galloway, Jeffers & Webster, 1976). In fact, our study has shown that when used chronically there is no significant change in CBF compared with pretreatment levels.

This study therefore provides another example of the fact that the chronic effects, certainly of this class of drugs, are often different from the acute changes. Physiological variables have been shown to change with the passage of time so that, for example, cardiac output decreases acutely but then returns to pretreatment levels in due course, and the same now appears true of CBF.

Although there is a current resurgence of interest in the ancillary properties of β-adrenergic receptor blockers we have been unable to show any significant differences in effect of CBF between drugs which do or do not possess these features. Similarly cardioselectivity on the one hand, and concurrent α-adrenoceptor blockade on the other, have not brought about any differences of note.

In conclusion it appears that β-adrenergic receptor blockers comply with the generalization stated by Sokoloff in 1959: 'The outstanding impression obtained from an overall view of the action of drugs on the cerebral circulation is the great resistance of the cerebral blood flow to change'.

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